European Journal of Medicinal Chemistry 46 (2011) 600–607

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Synthesis and antimicrobial activity of highly functionalised novel β-lactam grafted spiropyrrolidines and pyrrolizidines

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ARTICLE INFO

Article history:
Received 29 August 2010
Received in revised form
20 November 2010
Accepted 22 November 2010
Available online 1 December 2010

Keywords:
1,3-Dipolar cycloaddition
Azomethine ylide
β-Lactam
Pyrrolidine
Pyrrolizidine
Antimicrobial

ABSTRACT

A facile and one-pot synthesis of a series of novel spiropyrrolidines/pyrrolizidines with β-lactam substituent has been accomplished through 1,3-dipolar cycloaddition reaction of alkenyl esters derived from β-lactam aldehyde as dipolarophile with the dipole azomethine ylide derived from 1,2- and 1,3-diketones and secondary amino acids. The synthesized compounds were evaluated for antimicrobial activities and found to exhibit relatively good antibacterial activity at lower concentration against four human bacterial pathogens.

1. Introduction

1,3-Dipolar cycloaddition is one of the effective tools for the construction of five membered heterocycles [1]. Many important natural products have been effectively synthesized by this strategy since the reaction of 1,3-dipoles is often associated with regio- and stereo-selectivities [2–5]. Pyrrolidine based natural products are very useful in preventing and treating rheumatoid arthritis, asthma and allergies [6] and also possess anti-influenza virus [7] and anticonvulsant activities [8]. The azomethine ylide represents one of the most reactive and versatile classes of 1,3-dipoles and is readily trapped by a range of dipolarophiles forming substituted pyrrolidines [9]. Spiro compounds represent an important class of naturally occurring substances characterized by highly pronounced biological properties [10–12]. For example, spirotryprostatin A (Fig. 1), a natural product isolated from the fermentation broth of *Aspergillus fumigatus*, has been identified as a novel inhibitor of microtubule assembly [13]. Likewise, 1,3-indanediones have also captured much attention due to their important pharmacological properties [14] such as anti-inflammatory and anti-blood coagulation. Recently, our research group reported the synthesis and bioactivity of some of the spiropyrrolidines [15].

β-Lactam as synthetic intermediate has been widely recognized in organic synthesis [16] because it is an active moiety present in most widely used antibiotics such as penicillin [17], cephalosporins [18], carbapenems, nocardicins and monobactams which are also used as chemotherapeutic agents for treating microbial diseases [19]. Besides, it showed many other interesting biological properties, such as cholesterol absorption inhibitors [20], human cytomegalovirus protease inhibitors [21], thrombin inhibitors [22], anti-hyperglycemic [23], anti-tumour [24], anti-HIV [25], anti-inflammatory, analgesic activities [26] and serine-dependent enzyme inhibitors [27,28]. Hence, there has been renewed interest in the synthesis of such interesting β-lactam based heterocycles with potential applications.

Our research group has been largely involved in the synthesis of spiropyrrolidines/pyrrolizidines [29–31] and β-lactam substituted pyrrolidines [32] derivatives by intermolecular 1,3-dipolar cycloaddition. In this perspective, we had reported β-lactam substituted spiropyrrolidine/pyrrolizidine derivatives by intermolecular 1,3-dipolar cycloaddition [33] and macrocyclic bis-β-lactam through [2 + 2] Staudinger reaction [34]. Recently, we reported the synthesis of β-lactam substituted pyrroloisoquinoline and indolizinoindole ring system by intermolecular 1,3-dipolar cycloaddition [35]. In

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doi:10.1016/j.ejmech.2010.11.039

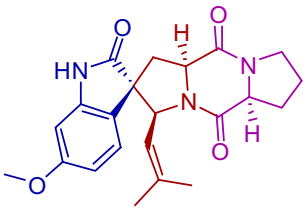


Fig. 1. Spirotryprostatin A.

addition, we have also reported the synthesis and antimicrobial activity of β-lactam fused spiroisoxazolidine chromanones/tetralones by intermolecular 1,3-dipolar cycloaddition recently [36].

Only few reports are available on the use of [3 + 2]-cycloaddition reaction as a tool to synthesize β-lactam based heterocycles [37–39]. It is noteworthy that in all these methods reported, β-lactam derivatives have been used extensively for the generation of 1,3-dipole but they have not been studied as a dipolarophile.

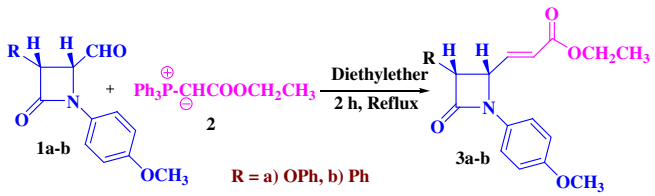
As a part of the ongoing research program on the synthesis of complex novel spiroheterocycles [40,41], herein we report for the first time, an expeditious and facile protocol for the synthesis of novel β-lactam substituted monospiropyrolidine/pyrrolizidines through 1,3-dipolar cycloaddition reaction of azomethine ylide generated from various di/triketones and secondary amino acids with alkenyl esters derived from β-lactam as dipolarophiles. The synthesized compounds were screened for antimicrobial activity and the results are presented in this paper.

2. Chemistry

(*E*)-Ethyl-3-(1-(4-methoxyphenyl)-4-oxo-3-phenylazetidin-2-yl) acrylate **3b** was synthesized for the first time by Wittig olefination reaction of β-lactam aldehyde [42] **1b** (Scheme 1). The geometry of the olefinic double bond was found to be *E* as evidenced by ^{1}H NMR spectra wherein the olefinic protons appeared δ 5.98 and 6.51 (J = 15.9 Hz).

We have explored the reactivity of β-lactam derivatives as efficient dipolarophiles for the synthesis of a rare class of β-lactam based spiroheterocycles. The azomethine ylide generated *in situ* from ninhydrin **4** and sarcosine **5**/L-proline **7** reacted with β-lactam derivatives **3a**–**b** as dipolarophiles to afford a series of novel β-lactam grafted monospiroindanopyrrolidines **6a**–**b**/pyrrolizidines **8a**–**b** (Scheme 2).

The structure and regiochemistry of the cycloadducts **6a**–**b** were established by IR, ^{1}H/^{13}C NMR spectroscopic and mass spectrometric studies. For instance, the IR spectrum of the cycloadduct **6a** showed four characteristic bands at 1740 cm^{-1}, 1703 cm^{-1}, 1739 cm^{-1} and 1725 cm^{-1} corresponding to the indane-1,3-dione ring carbonyls, the β-lactam ring carbonyl and ester carbonyl group respectively. The ^{1}H NMR spectrum of **6a**, showed a sharp singlet at δ 2.09 ppm for *N*-methyl protons. The H_a proton exhibited a doublet at δ 5.38 ppm (J = 5.4 Hz) and H_b proton resonated as a doublet of doublet at δ 4.77 ppm (J = 5.4 Hz, 6.9 Hz). The H_c proton appeared as a multiplet in the range δ 3.24–3.28 ppm and H_d proton exhibited a doublet at δ 3.52 ppm (J = 10.2 Hz). The ^{13}C NMR spectrum of **6a** showed a signal at δ 79.1 ppm for the spiro carbon and the signals at δ 199.4, 201.1 ppm and δ 162.5 ppm for the indane-1,3-dione and β-lactam carbonyl carbons, respectively. A peak at m/z 554 (M^+) in the mass spectrum of the compound **6a** confirmed the formation of cycloadduct.



Scheme 1.

Finally, the regio- and stereo-chemical outcome of the cycloaddition was unambiguously ascertained by single crystal X-ray diffraction analysis of the cycloadduct **8a** (Fig. 2) [43]. In the molecular structure of **8a**, the pyrrolidine ring adopts a twist conformation due to stabilization by intermolecular C–H···O hydrogen bonds.

Fascinated by the structural therapeutic diversities of spirooxindole ring such as antimicrobials, antitumourals, antibiotic agents, inhibitors of human NK-1 receptors [44] and antidiabetic [45], synthesis of β-lactam incorporated spirooxindolopyrrolidine/pyrrolizidine ring system was conceived as one of the targets for synthesis. Thus, the dipolarophiles **3a**–**b** when reacted with the azomethine ylide generated from isatin **9** and sarcosine **5**/L-proline **7** in refluxing acetonitrile, afforded β-lactam spirooxindolopyrrolidines **10a**–**b**/pyrrolizidines **11a**–**b** in moderate yield (Scheme 3). The formation of cycloadduct was confirmed by spectral and elemental analysis. In the IR spectrum of the compound **11a**, the amide carbonyl and ester carbonyl group exhibited a strong absorption bands at 1695 cm^{-1} and 1728 cm^{-1} respectively. The β-lactam amide carbonyl group appeared a strong absorption band at 1745 cm^{-1} and the NH group stretching was observed at 3395 cm^{-1}.

The ^{1}H NMR spectrum of the cycloadduct **11a** exhibited a multiplet in the range δ 1.64–2.36 for the pyrrolizidine ring methylene protons. The H_a proton appeared as a doublet at δ 5.87 ppm (J = 5.1 Hz) and H_b proton resonated as a doublet of doublet at δ 5.01 ppm (J = 5.1, 6.9 Hz). The H_d resonated as a doublet at δ 3.86 ppm (J = 10.2 Hz) and H_c proton exhibited a multiplet in the region δ 3.05–3.13 ppm. In ^{13}C NMR spectrum of cycloadduct **11a** showed a signal at δ 79.2 ppm for the spiro carbon and the signals at δ 178.1 ppm and 163.3 ppm were due to oxindole carbonyl carbon and β-lactam carbonyl carbon respectively. The ester carbonyl carbon resonated at δ 169.4 ppm. The mass spectrum of **11a** exhibited the molecular ion peak at m/z 567 (M^+).

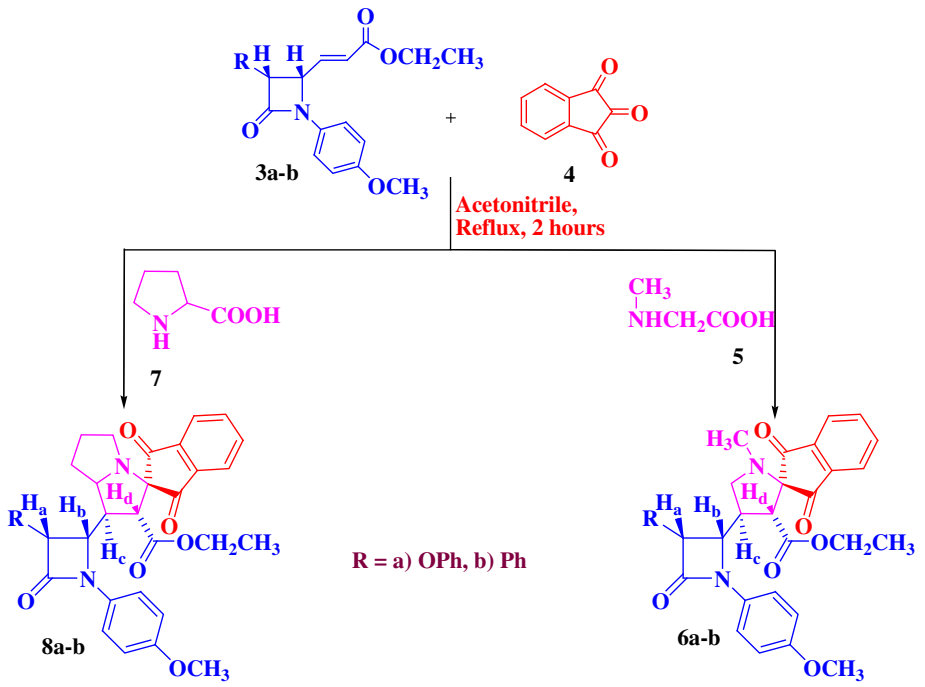
Finally, the regio- and stereo-chemical outcome of the cycloaddition reaction was unambiguously ascertained by single crystal X-ray analysis of the cycloadduct **11b** (Fig. 3). In the molecular structure of **11b**, the β-lactam molecule is planar and the pyrrolidine ring adopts a twist conformation. The molecular structure is stabilized by intermolecular C–H···O hydrogen bonds.

The biological significance of acenaphthenequinone based scaffolds [46] prompted us to synthesize spiropyrrolidines grafted acenaphthenequinone and β-lactam. Thus, the regioselective intermolecular cycloaddition of acenaphthequinone **12** and sarcosine **5**/L-proline **7** with dipolarophiles **3a**–**b** yielded spiroacenaphthenequinolopyrrolidines **13a**–**b**/pyrrolizidines **14a**–**b** in moderate yield (Scheme 4). The formation of the cycloadducts **13a**–**b** and **14a**–**b** was confirmed by spectral and elemental analysis.

To improve the yield, we carried out the reaction under different organic solvents such as toluene, dioxane and methanol but the reaction was found to give only poor yield of the products in all these solvents. After optimisations we have observed that acetonitrile was found to be the best solvent in terms of higher yield and shorter reaction times. A single regioisomer was isolated in all cases. No trace of the other regioisomers was found even after prolonged reaction times due to the steric hindrance between β-lactam and di/triketones.

3. Biology

The newly synthesized compounds **6a**–**b**, **8a**–**b**, **10a**–**b**, **11a**–**b**, **13a**–**b** and **14a**–**b** were evaluated for *in-vitro* antimicrobial activity



Scheme 2.

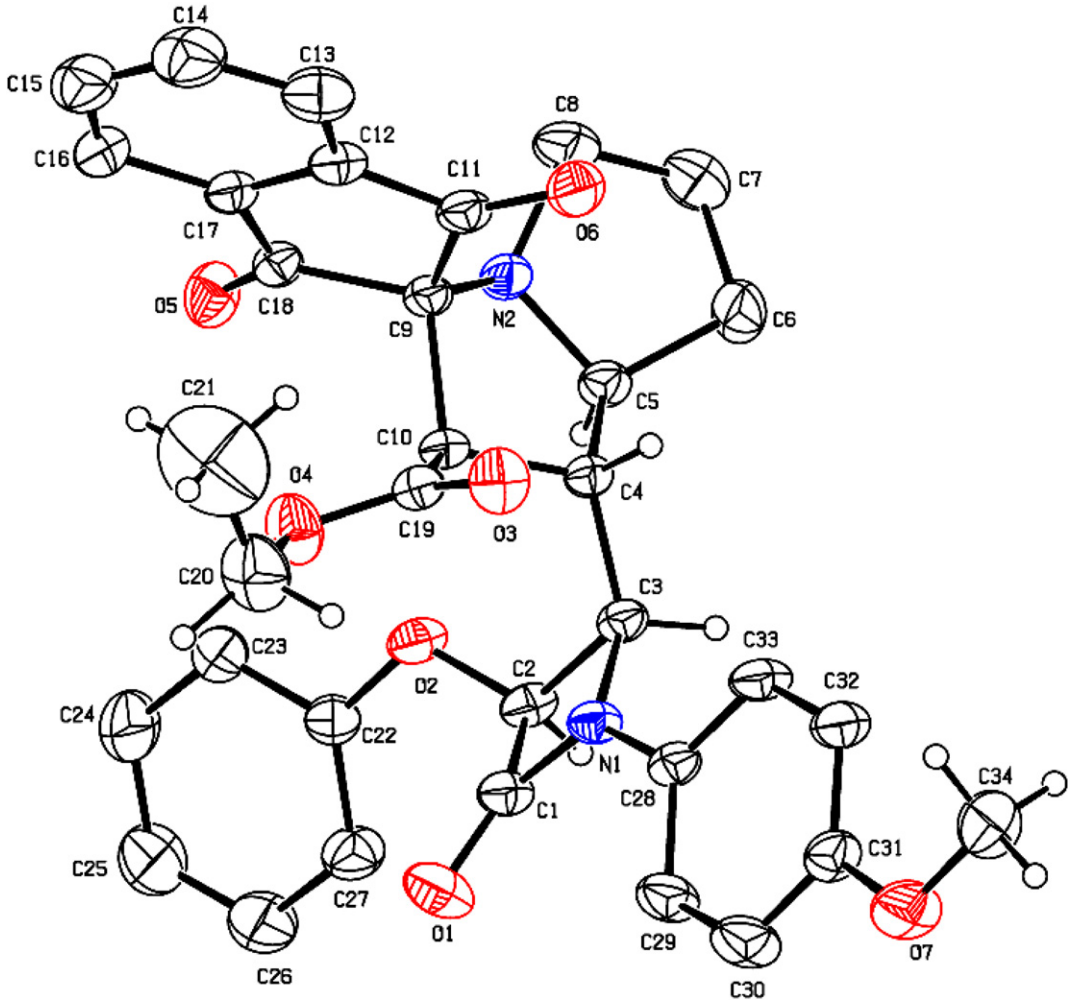
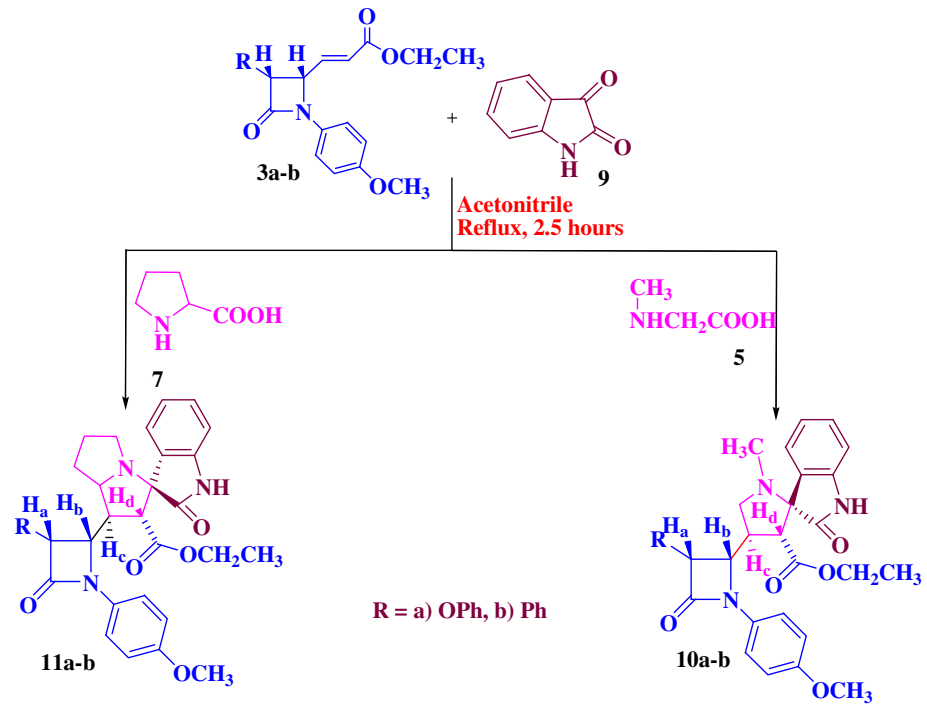


Fig. 2. ORTEP diagram of **8a**.



Scheme 3.

studies against microorganisms and results are discussed. The bioactivity studies were carried out against the bacteria, *Proteus mirabilis*, *Proteus vulgaris*, *Staphylococcus aureus*, *Salmonella typhi* which were obtained from (MUBL) Madras University Botany Laboratory,University of Madras, Chennai.

3.1. Antibacterial activity of β-lactam grafted spiropyrrolidines/pyrrolizidines (agar diffusion assay)

The agar diffusion method [47] was used for the determination of antibacterial activity of synthesized spiropyrrolidines/pyrrolizidines against microorganism listed above. About 9 ml of nutrient agar media were poured into petri plates (9 cm in diameter) and inoculated with respective test organism. Wells were made with cork borer on the solid agar and loaded with 25–100 mg/ml of the test compound with tetracycline as control. Petri dishes were incubated at 37 °C for 24 h and the average diameter of the inhibition zone surrounding the wells was measured after specified incubation period.

The antibacterial activity of the synthesized twelve β-lactam compounds against human bacterial pathogens as determined by agar diffusion method with tetracycline as reference control was investigated The maximum antimicrobial activity and inhibition zone were observed for compounds **10a**, **11a** and **11b** against the pathogen *P. mirabilis* while all other derivatives did not show good

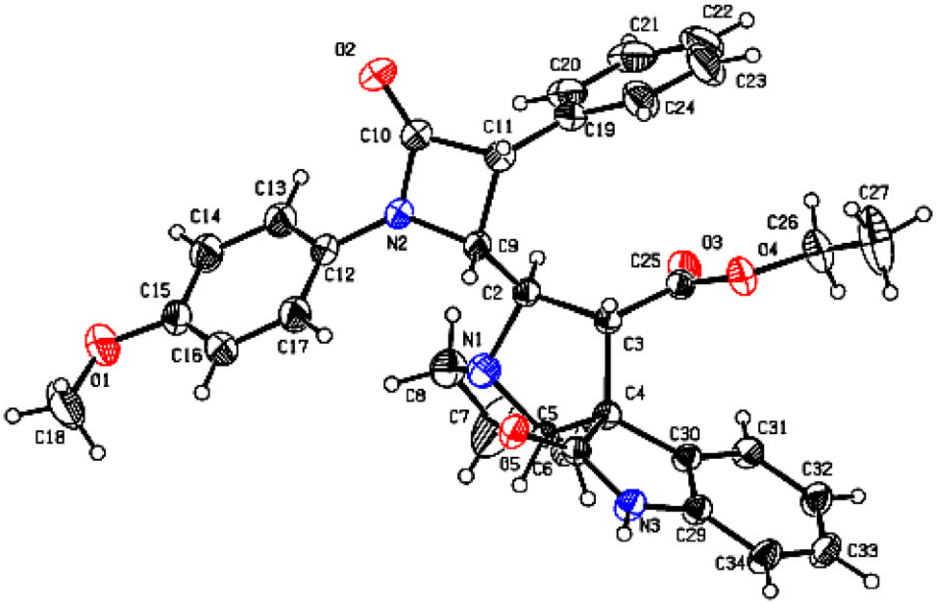
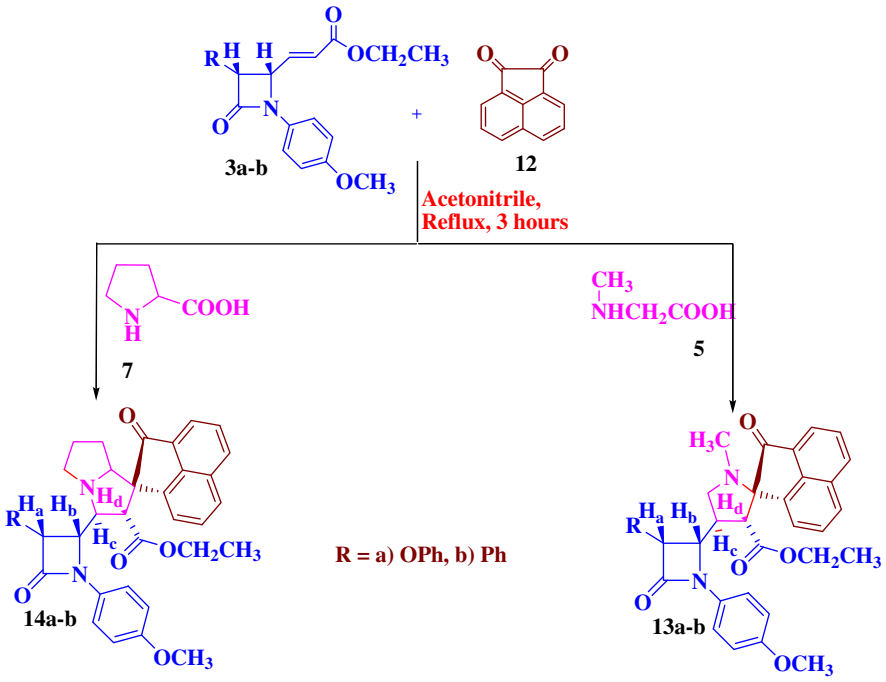


Fig. 3. ORTEP diagram of **11b**.



Scheme 4.

activity at low concentration. For *P. vulgaris* the compounds **11a** and **11b** showed very good antibacterial activity even at very low concentration as active as that of the reference compound tetracycline. The other compounds showed moderate antibacterial activity against the pathogen. The compounds **11a** and **11b** showed very good antimicrobial activity against the bacteria *S.aures* which is comparable to that of reference compound tetracycline. For the pathogen *S. typhi* the compounds **10a**, **11a** and **11b** showed good inhibitory activity, while **8a**, **8b** and **10b** showed moderate activity and all other compounds showed low activity against this pathogen. The oxindole derived compounds and nihydrin derived compounds showed good activity against all the pathogens in low concentration, which is comparable to the reference control. It was observed that all the antibacterial activities of the presently studied compounds are dose dependent. The oxindole derived compounds **11a**, **11b**, **10a** and **10b** were found to be effective in controlling all the test pathogens and particularly it control effectively in *P. vulgaris* and *P. mirabilis* than the rest of the compounds tested in the present study. The activity is very much comparable to the reference control. Ninhydrin derived compounds **8a** and **8b** exhibited good antibacterial activity against *P. vulgaris*, *P. Mirabilis* and *S. typhi* at higher concentration. The acenapthquinone derived compounds showed moderate antibacterial activity against *P. vulgaris* and *P. mirabilis* and ineffective in controlling *S. aureus* and *S. typhi* even in higher concentration. Further clinical studies are required to validate the effective compounds of the present study as an antimicrobial agent. The results are summarized in Tables 1–4.

4. Conclusion

In conclusion, we have successfully synthesized a series of novel β-lactam substituted monospiropyrrolidines/pyrrolizidines through intermolecular [3 + 2]-cycloaddition of azomethine ylide generated from di- and triketones and secondary amino acids with unusual dipolarophiles under different conditions. All the synthesized β-lactam substituted spiropyrrolidines/pyrrolizidines showed good antibacterial activity. The compounds **11a**, **11b**, **8a**, **8b** showed good activity against four human bacterial pathogens. The overall antibacterial activity of the synthesized compounds may be attributed to the presence of β-lactam substituent in all the compounds. The variation in bioactivity may be due to the presence of other spiro substituents present in the synthesized compounds.

5. Experimental

All melting points were uncorrected. IR spectra were recorded on a SHIMADZU 8300 series FT-IR instrument. ^{1}H NMR spectra were recorded in $CDCl_3$ using TMS as an internal standard on a JEOL GX 400 spectrometer at 400 MHz and on a BRUKER 300 spectrometer at 300 MHz ^{13}C NMR was recorded on a JEOL GX 400 spectrometer at 100 MHz and on a BRUKER 300 spectrometer at 75 MHz. Mass spectra were recorded on a JEOL DX 303 HF spectrometer. Elemental analysis was carried out on Perkin–Elmer 2400 instrument. Column chromatography was performed on silica gel

Table 1
Effect of spiro pyrrolidine/pyrrolizidines on the growth of human pathogen *Proteus mirabilis*.

Organism	Compound	Concentration of compounds(μg/ml)			
		25	50	75	100
		Zone of inhibition (mm)			
Proteus mirabilis	**6a**	9	13	16	18
	6b	11	13	14	18
	8a	8	15	18	22
	8b	10	15	16	23
	10a	12	13	22	32
	10b	11	14	18	21
	11a	12	16	24	36
	11b	14	18	21	32
	13a	9	11	15	20
	13b	–	9	13	18
	14a	10	13	16	20
	14b	9	11	14	18
	Tetracycline	18	24	28	>40

Table 2
Effect of spiro pyrrolidine/pyrrolizidines on the growth of human pathogen *Proteus vulgaris*.

Organism	Compound	Concentration of compounds (μg/ml)			
		25	50	75	100
		Zone of inhibition (mm)			
Proteus vulgaris	**6a**	12	16	20	23
	6b	11	14	18	21
	8a	9	18	23	26
	8b	12	17	20	24
	10a	11	14	18	21
	10b	11	14	16	20
	11a	19	20	27	>40
	11b	13	21	25	>40
	13a	9	11	15	20
	13b	–	10	15	21
	14a	9	11	16	20
	14b	–	12	17	20
	Tetracycline	18	24	28	>40

Table 4
Effect of spiro pyrrolidine/pyrrolizidines on the growth of human pathogen *Salmonella typhi*.

Organism	Compound	Concentration of compounds(μg/ml)			
		25	50	75	100
		Zone of inhibition (mm)			
Salmonella typhi	**6a**	9	11	13	19
	6b	–	9	13	18
	8a	11	15	17	23
	8b	9	12	14	20
	10a	11	14	20	28
	10b	12	15	21	29
	11a	13	16	21	31
	11b	11	14	18	26
	13a	9	11	14	16
	13b	–	11	13	18
	14a	–	9	18	19
	14b	–	13	14	18
	Tetracycline	18	22	28	>40

(ACME, 100–200 mesh). Routine monitoring of the reactions was made using thin layer chromatography developed on glass plates coated with silica gel-G (ACME) of 0.25 mm thickness and visualized with iodine. For anhydrous reactions, glasswares used were thoroughly dried in a hot air-oven, cooled and assembled under a stream of nitrogen. The organic extracts of crude products were dried over anhydrous $MgSO_4$. Solvents were reagent grade and were purified according to standard procedures. The starting materials ninhydrin, isatin, acenaphthenequinone, sarcosine and proline were purchased commercially and used as such.

5.1. General procedure for synthesis of azetidinyl ethyl acrylate, ***3a–b***

A mixture of β-lactam aldehyde **1a** (281 mg, 1 mmol), phosphonium ylide **2** (348 mg, 1 mmol) was refluxed for 2 h in diethyl ether. After completion of the reaction the solvent was removed under the vacuum. The crude product was then subjected to column chromatography using hexane:ethyl acetate (8.5:1.5) as eluent.

5.1.1. *(E)-Ethyl-3-[1-(4-methoxyphenyl)-4-oxo-3-phenoxy-azetidin-2-yl]acrylate (**3a**)*

Colorless solid; Yield 85%; mp 132 °C. IR (KBr): 1742, 1730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, CH_3, 3H); 3.79 (s, OCH_3, 3H); 4.12–4.19 (q, CH_2, 2H); 4.96 (t, 1H, $J = 6$ Hz); 5.48 (d, 1H, $J = 4.8$ Hz); 6.17 (d, 1H, $J = 15.9$ Hz); 6.87–6.97 (dd, 1H, $J = 6.9, 15.9$ Hz); 6.87–7.36 (m, 9H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 55.5, 58.8, 60.8, 81.5, 114.5, 115.7, 118.6, 122.6, 127.1, 129.6, 130.4, 140.0, 156.8, 157.1, 161.7, 164.9. Mass spectrum (EI, 70 eV): *m/z* 367.14 (M^+). Elemental Anal. Calcd. for $C_{21}H_{21}NO_5$: C, 68.63; H, 5.71; N, 3.81%. Found: C, 68.75; H, 5.83; N, 3.71%.

5.1.2. *(E)-Ethyl-3-[1-(4-methoxyphenyl)-4-oxo-3-phenyl-azetidin-2-yl] acrylate (**3b**)*

Colorless solid; Yield 85%; mp 127 °C. IR (KBr): 1745, 1731 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.15 (t, CH_3, 3H); 3.77 (s, OCH_3, 3H); 4.03–4.06 (q, CH_2, 2H); 4.87 (d, 1H, $J = 6$ Hz); 4.92 (t, 1H, $J = 6.3$ Hz); 5.98 (d, 1H, $J = 15.9$ Hz); 6.47–6.55 (dd, 1H, $J = 6.9, 15.9$ Hz); 6.85–7.38 (m, 9H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 55.5, 57.0, 59.4, 60.5, 114.4, 117.9, 118.3125.7, 128.0, 128.5, 128.7, 129.9, 129.2, 131.1, 142.7, 156.4, 164.2, 164.8. Mass spectrum (EI, 70 eV): *m/z* 351.15 (M^+). Elemental Anal. Calcd. for $C_{21}H_{21}NO_4$: C, 71.76; H, 5.98; N, 3.98%. Found: C, 71.90; H, 5.84; N, 3.88%.

Table 3
Effect of spiropyrrolidine/pyrrolizidines on the growth of human pathogen *Staphylococcusi aureus*.

Organism	Compound	Concentration of compounds (μg/ml)			
		25	50	75	100
		Zone of inhibition (mm)			
Staphylococcusi aureus	**6a**	11	13	16	18
	6b	11	15	18	22
	8a	9	14	18	24
	8b	9	13	16	28
	10a	14	19	21	26
	10b	14	18	23	27
	11a	14	18	22	34
	11b	9	16	21	31
	13a	–	9	15	19
	13b	–	10	15	21
	14a	–	11	14	18
	14b	9	14	19	21
	Tetracycline	18	22	28	>40

5.2. General procedure for synthesis of cycloadducts, ***6a–b*** and ***8a–b***

To a solution of ninhydrin **4** (160 mg, 1 mmol), sarcosine **5** (89 mg, 1 mmol)/L-proline **7** (115 mg, 1 mmol) in dry acetonitrile (10 mL) was added azetidinyl ethyl acrylate **3a** (351 mg, 1 mmol) under nitrogen atmosphere. The solution was refluxed for 2 h and solvent was distilled off under reduced pressure. The crude product was purified by column chromatography using hexane:ethyl acetate (8:2) as eluent.

5.2.1. *1-N-Methyl spiro(2.2′)indandione-3-ethoxycarbonyl-4-[(1″-N-p-methoxyphenyl)-3″-phenoxy-azetidine-2″-one] pyrrolidine (**6a**)*

Colorless solid; Yield 86%; mp 155 °C. IR (KBr): 1740, 1739, 1725 and 1703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.54 (t, CH_3, 3H); 2.09 (s, NCH_3, 3H); 3.24–3.28 (m, 1H); 3.31 (m, NCH_2, 2H); 3.52 (d, 1H, $J = 10.2$ Hz); 3.70 (s, OCH_3, 3H); 3.72–3.77 (q, 2H); 4.77 (dd, 1H, $J = 5.4, 6.9$ Hz), 5.38 (d, 1H, $J = 5.4$ Hz), 6.79–7.95 (m, 13H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.7, 21.3, 30.6, 37.9, 54.9, 55.2, 59.7, 73.3, 79.1, 113.2, 114.8, 120.4, 121.0, 121.3, 128.3, 128.7, 134.8, 135.0, 139.9, 140.4, 155.5, 156.5, 162.5, 168.1, 199.4, 201.1. Mass spectrum (EI, 70 eV): *m/z* 554 (M^+). Elemental Anal. Calcd. for $C_{32}H_{30}N_2O_7$: C, 69.30; H, 5.45; N, 5.05%. Found: C, 69.42; H, 5.52; N, 5.15%.

*5.2.2. 1-N-Methyl-spiro(2.2′)indandione-3-ethoxycarbonyl-4-[(1″-N-4-methoxyphenyl)-3″-phenylazetidine-2″-one] pyrrolidine (**6b**)*

Colorless solid; Yield 85%; mp 144 °C. IR (KBr): 1741, 1739, 1726 and 1703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.52 (t, CH_3, 3H); 2.10 (s, NCH_3 3H); 3.25–3.29 (m, 1H); 3.36 (m, NCH_2, 2H); 3.47 (d, 1H, J = 9.8 Hz); 3.73 (s, OCH_3, 3H); 3.76–3.81 (q, 2H); 4.69 (t, 1H, J = 5.7 Hz); 4.74 (d, 1H, J = 5.7 Hz); 6.81–8.05 (m, 13H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.1, 22.8, 31.4, 39.7, 54.7, 55.4, 60.8, 74.1, 79.7, 113.6, 114.3, 122.2, 122.6, 123.1, 128.1, 128.9, 135.8, 136.1, 138.3, 140.9, 153.7, 157.0, 164.0, 168.5, 199.9, 201.3. Mass spectrum (EI, 70 eV): m/z 538 (M^+). Elemental Anal. Calcd. for $C_{32}H_{30}N_2O_6$: C, 71.36; H, 5.61; N, 5.20%. Found: C, 71.47; H, 5.79; N, 5.32%.

*5.2.3. Spiro(2.2′)indandione-3-ethoxycarbonyl-4-[(1″-N-4-methoxyphenyl)-3″-phenoxy-azetidine-2″-one]pyrrolizidine (**8a**)*

Orange red crystals; Yield 89%; mp 163 °C. IR (KBr): 1741, 1739, 1725 and 1703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.70 (t, CH_3, 3H); 1.69–2.59 (m, 7H); 3.53–3.60 (m, 1H); 3.66 (d, 1H, J = 10.2 Hz); 3.81 (s, OCH_3, 3H); 3.88 (q, 2H); 5.0 (t, 1H, J = 5.4 Hz); 5.41(d, 1H, J = 5.4 Hz); 6.94–7.94 (m, 13H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.1, 28.3, 31.5, 47.9, 55.4, 57.4, 58.7, 61.2, 67.3, 73.2, 80.1, 114.6, 115.8, 120.5, 122.3, 122.6, 123.5, 129.6, 130.2, 136.0, 136.2, 140.9, 141.8, 157.1, 163.9, 169.4, 201.6, 201.8. Mass spectrum (EI, 70 eV): m/z 580 (M^+). Elemental Anal. Calcd. for $C_{34}H_{32}N_2O_7$: C, 70.33; H, 5.56; N, 4.82%. Found: C, 70.41; H, 5.42; N, 4.77%.

*5.2.4. Spiro(2.2′)indandione-3-ethoxycarbonyl-4-[(1″-N-4-methoxyphenyl)-3″-phenyl azetidine-2″-one]-pyrrolizidine (**8b**)*

Pale yellow solid; Yield 87%; mp 148 °C. IR (KBr): 1740, 1739, 1725 and 1703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.71 (t, CH_3, 3H); 1.09–2.44 (m, 7H); 3.03–3.09 (m, 1H); 3.58 (d, 1H, J = 10.2 Hz); 3.71 (q, 2H); 3.83 (s, OCH_3, 3H); 4.84 (t, 1H, J = 6 Hz); 4.95 (d, 1H, J = 5.7 Hz); 6.95–8.01 (m, 13H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.1, 27.6, 29.6, 30.8, 47.7, 55.5, 57.9, 58.7, 61.1, 67.2, 73.1, 114.6, 121.2, 122.7, 123.7, 127.9, 128.7, 129.7, 130.9, 132.8, 136.1, 140.9, 141.5, 157.0, 166.5, 169.3, 201.2, 201.4. Mass spectrum (EI, 70 eV): m/z 564 (M^+). Elemental Anal. Calcd. for $C_{34}H_{32}N_2O_6$: C, 72.32; H, 5.71; N, 4.96%. Found: C, 72.38; H, 5.64; N, 4.84%.

*5.3. General procedure for synthesis of cycloadducts, **10a–b** and **11a–b***

To a solution of isatin **9** (147 mg, 1 mmol), sarcosine **5** (89 mg, 1 mmol)/L-proline **7** (115 mg, 1 mmol) in dry acetonitrile (10 ml) was added azetidinyl ethyl acrylate **3a** (351 mg, 1 mmol) under nitrogen atmosphere. The solution was refluxed for 2.5 h and solvent was distilled off under reduced pressure. The crude product was purified by column chromatography using hexane:ethyl acetate (8:2) as eluent.

*5.3.1. 1-N-Methyl spiro(2.3′)oxindolo-3-ethoxycarbonyl-4-[(1″-N-4-methoxyphenyl)-3″-phenoxy-azetidine-2″-one] pyrrolidine (**10a**)*

Colorless solid; Yield 86%; mp 168 °C. IR (KBr): 3396, 1742, 1730 and 1696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.68 (t, CH_3, 3H); 2.11 (s, NCH_3, 3H); 3.25–3.30 (m, NCH_2, 2H); 3.45–3.52 (m, 1H); 3.58 (q, 2H); 3.68 (d, 1H, J = 10.2 Hz); 3.86 (s, OCH_3, 3H); 4.98 (t, 1H, J = 5.7 Hz); 5.25 (d, 1H, J = 5.7 Hz); 6.95–7.86 (m, 13H, Ar-H); 10.27 (brs, NH, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.2, 24.6, 34.8, 55.9, 56.5, 55.9, 56.2, 61.6, 74.2, 79.8, 109.8, 115.2, 122.5, 122.8, 125.5, 125.6, 128.1, 129.1, 129.3, 129.4, 129.9, 132.6, 140.8, 157.1, 166.0, 169.3, 179.0. Mass spectrum (EI, 70 eV): m/z 541 (M^+). Elemental Anal. Calcd. for $C_{31}H_{31}N_3O_6$: C, 68.75; H, 5.77; N, 7.76%. Found: C, 68.86; H, 5.83; N, 7.84%.

*5.3.2. 1-N-Methyl spiro(2.3′)oxindolo-3-ethoxycarbonyl-4-[(1″-N-4-methoxyphenyl)-3″-phenylazetidine-2″-one]pyrrolidine (**10b**)*

Colorless solid; Yield 84%; mp 142 °C. IR (KBr): 3395, 1743, 1730 and 1695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.61 (t, CH_3, 3H); 2.03 (s, NCH_3, 3H); 2.90–2.95 (m, NCH_2, 2H); 3.14–3.16 (m, 1H); 3.24 (d, 1H, J = 10.2 Hz); 3.46 (q, 2H); 3.81 (s, OCH_3, 3H); 4.76 (t, 1H, J = 5.7 Hz); 4.98 (d, 1H, J = 5.7 Hz); 6.82–7.74 (m, 13H, Ar-H); 8.54 (s, 1H, N–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.2, 35.2, 40.8, 55.4, 55.7, 56.5, 57.5, 60.3, 60.9, 73.4, 109.9, 114.4, 122.2, 122.8, 125.6, 125.9, 127.8, 128.7, 129.0, 129.3, 129.9, 130.1, 141.1, 157.4, 166.9, 169.4, 179.3. Mass spectrum (EI, 70 eV): m/z 525 (M^+). Elemental Anal. Calcd. for $C_{31}H_{31}N_3O_5$: C, 70.84; H, 5.94; N, 7.99%. Found: C, 70.93; H, 5.86; N, 7.88%.

*5.3.3. Spiro(2.3′)oxindolo-3-ethoxycarbonyl-4-[(1″-N-4-methoxyphenyl)-3″-phenoxy-azetidine-2″-one]-pyrrolizidine (**11a**)*

Colorless crystals; Yield 89%; mp 220 °C. IR (KBr): 3395, 1745, 1728 and 1695 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 0.62 (t, CH_3, 3H); 1.64–2.36 (m, 7H); 3.05–3.13 (m, 1H); 3.61 (q, 2H); 3.83 (s, OCH_3, 3H); 3.86 (d, 1H, J = 10.2 Hz); 5.01 (dd, 1H, J = 5.1, 6.9 Hz); 5.87 (d, 1H, J = 5.1 Hz); 6.82–7.79 (m, 13H, Ar-H); 10.46 (s, 1H, N–H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 13.0, 27.5, 31.5, 44.7, 46.8, 55.3, 57.7, 57.9, 59.9, 65.2, 72.0, 79.2, 109.7, 114.4, 115.3, 118.7, 119.8, 120.8, 125.2, 125.6, 129.3, 129.5, 129.6, 130.5, 142.7, 156.9, 163.3, 169.4, 178.1. Mass spectrum (EI, 70 eV): m/z 567 (M^+). Elemental Anal. Calcd. for $C_{33}H_{33}N_3O_6$: C, 69.83; H, 5.86; N, 7.40%. Found: C, 69.97; H, 5.75; N, 7.31%.

*5.3.4. Spiro(2.3′)oxindolo-3-ethoxycarbonyl-4-[(1″-N-4-methoxyphenyl)-3″-phenylazetidine-2″-one]-pyrrolizidine (**11b**)*

Colorless crystals; Yield 87%; mp 225 °C. IR (KBr): 3395, 1745, 1732 and 1698 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 0.75 (t, CH_3, 3H); 1.38–2.62 (m, 7H); 2.68–2.74 (m, 1H); 3.63 (q, 2H); 3.67 (d, 1H, J = 9.8 Hz); 3.74 (s, OCH_3, 3H); 5.03 (t, 1H, J = 5.7 Hz); 5.06 (d, 1H, J = 5.7 Hz); 6.49–7.60 (m, 13H, Ar-H); 10.50 (brs, 1H, N–H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 13.1, 27.2, 31.0, 40.1, 46.5, 55.3, 57.2, 57.3, 59.9, 64.9, 71.6, 78.5, 109.8, 114.3, 120.7, 120.8, 125.1, 125.3, 127.7, 128.4, 129.3, 129.7, 131.1, 133.5, 142.8, 156.2, 165.8, 169.6, 178.2. Mass spectrum (EI, 70 eV): m/z 551 (M^+). Elemental Anal. Calcd. for $C_{33}H_{33}N_3O_5$: C, 71.85; H, 6.03; N, 7.62%. Found: C, 71.97; H, 6.14; N, 7.54%.

*5.4. General procedure for synthesis of cycloadducts, **13a–b** and **14a–b***

To a solution of acenaphthequinone **12** (182 mg, 1 mmol), sarcosine **5** (89 mg, 1 mmol)/L-proline **7** (115 mg, 1 mmol) in dry acetonitrile (10 ml) azetidinyl ethyl acrylate **3a** (351 mg, 1 mmol) was added under N_2 atmosphere. The solution was refluxed for 3 h and solvent was distilled off under reduced pressure. The crude product was purified by column chromatography using hexane:ethyl acetate (8:2) as eluent.

*5.4.1. 1-N-Methyl spiro(2.2′)acenaphtheno-3-ethoxy-carbonyl-4-[(1″-N-4-methoxy-phenyl)-3″-phenoxy-azetidine-2″-one] pyrrolidine (**13a**)*

Colorless solid; Yield 79%; mp 277 °C. IR (KBr): 1747, 1729 and 1706 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 0.70 (t, CH_3, 3H); 2.22 (s, NCH_3, 3H); 3.02–3.07 (m, 1H); 3.46–3.49 (m, NCH_2, 2H); 3.68 (d, 1H, J = 9.8 Hz), 3.76 (s, OCH_3, 3H); 3.89 (q, 2H); 4.88–4.93 (dd, 1H, J = 5.4, 9 Hz); 5.53 (d, 1H, J = 5.4 Hz); 6.85–8.16 (m, 15H, Ar-H,). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 22.6, 35.4, 40.0, 55.4, 56.3, 57.0, 59.9, 61.1, 80.5. 114.4, 116.1, 121.3, 122.4, 122.5, 125.5, 128.0, 128.2, 129.5, 129.6, 130.5, 131.9, 156.9, 157.8, 163.7, 169.6, 201.5. Mass spectrum (EI, 70 eV): m/z 576 (M^+). Elemental Anal. Calcd. for $C_{35}H_{32}N_2O_6$: C, 72.90; H, 5.59; N, 4.86%. Found: C, 72.98; H, 5.45; N, 4.97%.

*5.4.2. 1-N-Methyl spiro(2.2′)acenaphtheno-3-ethoxy-carbonyl-4-[(1″-N-4-methoxyphenyl)-3″-phenyl-azetidine-2″-one]pyrrolidine (**13b**)*

Colorless solid; Yield 78%; mp 198 °C. IR (KBr): 1740, 1733 and 1705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 0.68 (t, CH_3, 3H); 2.21 (s, NCH_3, 3H); 3.02–3.08 (m, 1H); 3.21–3.26 (m, NCH_2, 2H); 3.39 (q, 2H); 3.54 (d, 1H, $J = 9.2$ Hz); 3.72 (s, OCH_3, 3H); 4.54 (t, 1H, $J = 5.7$ Hz); 4.97 (d, 1H, $J = 5.7$ Hz); 6.65–7.87 (m, 15H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.1, 22.6, 34.2, 39.7, 55.3, 56.0, 57.2, 58.8, 61.3, 79.8, 114.7, 116.0, 120.6, 121.9, 122.5, 125.3, 127.4, 127.8, 128.1, 128.3, 130.1, 131.1, 156.8, 157.2164.3, 170.5, 204.9. Mass spectrum (EI, 70 eV): m/z 560 (M^+). Elemental Anal. Calcd. for $C_{35}H_{32}N_2O_5$: C, 74.98; H, 5.75; N, 5.00%. Found: C, 74.85; H, 5.81; N, 5.13%.

*5.4.3. Spiro(2.3′)acenaphtheno-3-ethoxycarbonyl-4-[(1″-N-4-methoxyphenyl)-3″-phenoxy-azetidine-2″-one] pyrrolizidine (**14a**)*

Colorless solid; Yield 84%; mp 176 °C. IR (KBr): 1749, 1730 and 1705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.73 (t, 3H); 1.15–2.35 (m, 7H); 3.32 (m, 1H); 3.70 (s, OCH_3, 3H); 3.85 (d, 1H, $J = 10.8$ Hz); 4.01–12 (q, 2H); 4.90 (t, 1H, $J = 5.7$ Hz); 5.38 (d, 1H, $J = 5.7$ Hz), 6.83–7.98 (m, 15H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.5, 28.0, 29.0, 45.9, 47.6, 55.3, 56.0, 58.8, 59.9, 66.1, 79.8, 80.8, 114.7, 121.8, 122.5, 125.3, 127.4, 127.9, 128.1, 128.4, 130.1, 131.6, 132.2, 135.9, 143.1, 157.7, 166.3, 170.5, 205.8. Mass spectrum (EI, 70 eV): m/z 602 (M^+). Elemental Anal. Calcd. for $C_{37}H_{34}N_2O_6$: C, 73.74; H, 5.69; N, 4.65%. Found: C, 73.83; H, 5.58; N, 4.57%.

*5.4.4. Spiro(2.3′)acenaphtheno-3-ethoxycarbonyl-4-[(1″-N-4-methoxyphenyl)-3″-phenyl-azetidine-2″-one] pyrrolizidine (**14b**)*

Colorless solid; Yield 82%; mp 222 °C. IR (KBr): 1746, 1725 and 1704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.72 (t, 3H); 1.04–2.53 (m, 7H); 3.27–3.31 (m, 1H); 3.69 (s, OCH_3, 3H); 3.74 (d, 1H, $J = 10.2$ Hz); 3.81(q, 2H); 4.00 (t, 1H, $J = 5.7$ Hz); 4.88 (d, 1H, $J = 5.7$ Hz); 6.76–7.95 (m, 15H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 12.6, 27.7, 31.5, 46.2, 54.0, 54.1, 58.4, 55.7, 54.5, 59.6, 60.1, 81.1, 114.5, 121.9, 122.5, 125.3, 127.4, 127.8, 127.9, 128.6, 130.1, 131.6, 132.2, 135.4, 143.2, 156.8, 166.3, 170.5, 204.9. Mass spectrum (EI, 70 eV): m/z 586 (M^+). Elemental Anal. Calcd. for $C_{37}H_{34}N_2O_5$: C, 75.75; H, 5.84; N, 4.77%. Found: C, 75.86; H, 5.95; N, 4.65%.

Acknowledgements

The authors thank Council of Scientific and Industrial Research (CSIR), New Delhi, India for financial support. One of the authors N.A. thanks Council of Scientific and Industrial Research (CSIR), New Delhi, for the award of Junior Research Fellowship (JRF) and Senior Research Fellowship (SRF). The Department of Science and Technology (DST-FIST) is also thanked for NMR spectra.

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